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NEWS 2	MAR 31	IFICDB, IFIPAT, and IFIUDB enhanced with new custom IPC display formats
NEWS 3	MAR 31	CAS REGISTRY enhanced with additional experimental spectra
NEWS 4	MAR 31	CA/CAplus and CASREACT patent number format for U.S. applications updated
NEWS 5	MAR 31	LPCI now available as a replacement to LDPCI
NEWS 6	MAR 31	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 7	APR 04	STN AnaVist, Version 1, to be discontinued
NEWS 8	APR 15	WPIDS, WPINDEX, and WPIX enhanced with new predefined hit display formats
NEWS 9	APR 28	EMBASE Controlled Term thesaurus enhanced
NEWS 10	APR 28	IMSRESEARCH reloaded with enhancements
NEWS 11	MAY 30	INPAFAMDB now available on STN for patent family searching
NEWS 12	MAY 30	DGENE, PCTGEN, and USGENE enhanced with new homology sequence search option
NEWS 13	JUN 06	EPFULL enhanced with 260,000 English abstracts
NEWS 14	JUN 06	KOREAPAT updated with 41,000 documents
NEWS 15	JUN 13	USPATFULL and USPAT2 updated with 11-character patent numbers for U.S. applications
NEWS 16	JUN 19	CAS REGISTRY includes selected substances from web-based collections
NEWS 17	JUN 25	CA/CAplus and USPAT databases updated with IPC reclassification data
NEWS 18	JUN 30	AEROSPACE enhanced with more than 1 million U.S. patent records
NEWS 19	JUN 30	EMBASE, EMBAL, and LEMBASE updated with additional options to display authors and affiliated organizations
NEWS 20	JUN 30	STN on the Web enhanced with new STN AnaVist Assistant and BLAST plug-in
NEWS 21	JUN 30	STN AnaVist enhanced with database content from EPFULL
NEWS 22	JUL 28	CA/CAplus patent coverage enhanced
NEWS 23	JUL 28	EPFULL enhanced with additional legal status information from the epoline Register
NEWS 24	JUL 28	IFICDB, IFIPAT, and IFIUDB reloaded with enhancements
NEWS 25	JUL 28	STN Viewer performance improved

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FILE LAST UPDATED: 30 Jul 2008  (20080730/ED)

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=> antibody
        333216 ANTIBODY
        399810 ANTIBODIES
L1      529466 ANTIBODY
                 (ANTIBODY OR ANTIBODIES)

=> gp120 (l) CD4
          6860 GP120
         63387 CD4
L2        2799 GP120 (L) CD4

=> complex
       1424677 COMPLEX
        779802 COMPLEXES
```

```
L3     1732922 COMPLEX
                  (COMPLEX OR COMPLEXES)

=> gp160 (l) CD4
          1488 GP160
         63387 CD4
L4          444 GP160 (L) CD4

=> L2 and L3
L5          608 L2 AND L3

=> L4 and L3
L6          108 L4 AND L3

=> L1 and L5
L7          292 L1 AND L5

=> L1 and L6
L8           43 L1 AND L6

=> complex (p) L2
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'COMPLEX (P) L2'
       1424677 COMPLEX
        779802 COMPLEXES
       1732922 COMPLEX
                  (COMPLEX OR COMPLEXES)
L9          608 COMPLEX (P) L2

=> L1 and L9
L10         292 L1 AND L9

=> (gp120 complexed with CD4)
          6860 GP120
         35929 COMPLEXED
         63387 CD4
L11          2 (GP120 COMPLEXED WITH CD4)
                  (GP120(W)COMPLEXED(1W)CD4)

=> L1 and L11
L12          2 L1 AND L11

=> D L12 IBIB ABS 1-2

L12  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2003:790182  CAPLUS
DOCUMENT NUMBER:         140:144270
TITLE:                   Analysis of the immunogenic properties of a
                         single-chain polypeptide analogue of the HIV-1
                         gp120-CD4 complex in transgenic mice that produce
                         human immunoglobulins
AUTHOR(S):               He, Yuxian; D'Agostino, Paul; Pinter, Abraham
CORPORATE SOURCE:        Laboratory of Retroviral Biology, Public Health
                         Research Institute, Newark, NJ, 07103-3506, USA
SOURCE:                  Vaccine (2003), 21(27-30), 4421-4429
                         CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER:               Elsevier Science Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The potential utility of gp120 complexed to
     CD4 in HIV-1 vaccine development has been shown by studies in
```

which such complexes were able to induce antibodies to cryptic gp120 epitopes and to generate broadly neutralizing humoral responses. Recently, a full-length single-chain (FLSC) analog of the gp120-CD4 receptor complex, consisting of HIV-1 Bal gp120 joined to the D1D2 domains of CD4 by a 20-amino-acid linker, has been described. We tested the immunogenicity of this protein in transgenic XMG2 XenoMouse mice that express human IgG2 with κ light chain loci and that model human humoral immune responses. Six mice immunized with purified FLSC all developed high antibody titers for the immunogen, but none of the sera possessed neutralizing activities against HIVBaL or HIVSF162 virus. A panel of 39 human monoclonal antibodies (mAbs) were generated from an immunized mouse. Only three of these mAbs recognized linear epitopes. One of these mapped to the V3 region and two to the C-terminus of gp120. The majority of the mAbs (36/39) were directed against one of two distinct conformational epitopes specific for FLSC. Binding of representative mAbs to these epitopes was not blocked by antibodies to a number of known targets on gp120, but was enhanced by binding of 17b, directed to a CD4-induced epitope on gp120. None of the FLSC-induced mAbs possessed neutralization activity against either HIV-1 BaL or SF162. These results suggest that a major portion of the antibody response against the FLSC protein may be directed against immunodominant conformational epitopes unique to the fusion protein that do not mediate viral neutralization. This property may limit the utility of this chimeric mol. as an HIV-1 vaccine candidate.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1998:785567 CAPLUS
DOCUMENT NUMBER: 130:37291
TITLE: HIV immunogenic complexes
INVENTOR(S): Devico, Anthony L.; Pal, Ranajit; Sarngadharan, Mangalasseril G.
PATENT ASSIGNEE(S): Akzo Nobel N.V., Neth.
SOURCE: U.S., 16 pp., Cont.-in-part of U.S. 5,518,723. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5843454	A	19981201	US 1995-464680	19951220
WO 9426305	A1	19941124	WO 1994-US5020	19940506
W: AU, CA, FI, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6328973	B1	20011211	US 2000-479675	20000107
US 6465172	B1	20021015	US 2001-905963	20010717
US 20030039663	A1	20030227	US 2001-905962	20010717
US 20040076636	A1	20040422	US 2003-612192	20030702

PRIORITY APPLN. INFO.:	US 1993-60926	A2	19930507
	WO 1994-US5020	W	19940506
	US 1995-464680	A3	19951220
	US 1998-75544	A3	19980511
	US 2000-479675	A3	20000107
	US 2001-905962	A2	20010717

AB A vaccine and a method of raising neutralizing antibodies against HIV infection. The vaccine comprises a complex of gp120 covalently bonded to CD4 or to succinyl Con A. Also disclosed are immunol. tests using the complex or antibody thereto for detection of HIV

infection. The vaccine composition may also comprises immune adjuvant such as aluminum phosphate gel.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D L8 IBIB ABS Ti 1-15

L8 ANSWER 1 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:241047 CAPLUS
DOCUMENT NUMBER: 146:400385
TITLE: Specific amino acids in the N-terminus of the gp41 ectodomain contribute to the stabilization of a soluble, cleaved gp140 envelope glycoprotein from human immunodeficiency virus type 1
AUTHOR(S): Dey, Antu K.; David, Kathryn B.; Klasse, Per J.; Moore, John P.
CORPORATE SOURCE: Department of Microbiology and Immunology, Weill Medical College of Cornell University, New York, NY, 10021, USA
SOURCE: Virology (2007), 360(1), 199-208
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The HIV-1 envelope glycoprotein is expressed on the viral membrane as a trimeric complex, formed by three gp120 surface glycoproteins non-covalently associated with three membrane-anchored gp41 subunits. The labile nature of the association between gp120 and gp41 hinders the expression of soluble, fully cleaved, trimeric gp140 proteins for structural and immunization studies. Disruption of the primary cleavage site within gp160 allows the production of stable gp140 trimers, but cleavage-defective trimers are antigenically dissimilar from their cleaved counterparts. Soluble, stabilized, proteolytically cleaved, trimeric gp140 proteins can be generated by engineering an intermol. disulfide bond between gp120 and gp41 (SOS), combined with a single residue change, I559P, within gp41 (SOSIP). The authors have found that SOSIP gp140 proteins based on the subtype A HIV-1 strain KNH1144 form particularly homogenous trimers compared to a prototypic strain (JR-FL, subtype B). The authors now show that the determinants of this enhanced stability are located in the N-terminal region of KNH11144 gp41 and that, when substituted into heterologous Env sequences (e.g., JR-FL and Ba-L) they have a similarly beneficial effect on trimer stability. The stabilized trimers retain the epitopes for several neutralizing antibodies (b12, 2G12, 2F5 and 4E10) and the CD4-IgG2 mol., suggesting that the overall antigenic structure of the gp140 protein has not been adversely impaired by the trimer-stabilizing substitutions. The ability to increase the stability of gp140 trimers might be useful for neutralizing antibody-based vaccine strategies based on the use of this type of immunogen.
TI Specific amino acids in the N-terminus of the gp41 ectodomain contribute to the stabilization of a soluble, cleaved gp140 envelope glycoprotein from human immunodeficiency virus type 1
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:1087705 CAPLUS
DOCUMENT NUMBER: 146:22123
TITLE: Restraining the conformation of HIV-1 gp120 by removing a flexible loop

AUTHOR(S): Rits-Volloch, Sophia; Frey, Gary; Harrison, Stephen C.; Chen, Bing
CORPORATE SOURCE: Laboratory of Molecular Medicine, Children's Hospital, Boston, MA, USA
SOURCE: EMBO Journal (2006), 25(20), 5026-5035
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The trimeric HIV/SIV envelope glycoprotein, gp160, is cleaved to noncovalently associated fragments, gp120 and gp41. Binding of gp120 to viral receptors leads to large structural rearrangements in both fragments. The unliganded gp120 core has a disordered β3-β5 loop, which reconfigures upon CD4 binding into an ordered, extended strand. Mol. modeling suggests that residues in this loop may contact gp41. We show here that deletions in the β3-β5 loop of HIV-1 gp120 weaken the binding of CD4 and prevent formation of the epitope for monoclonal antibody (mAb) 17b (which recognizes the coreceptor site). Formation of an encounter complex with CD4 binding and interactions of gp120 with mAbs b12 and 2G12 are not affected by these deletions. Thus, deleting the β3-β5 loop blocks the gp120 conformational change and may offer a strategy for design of restrained immunogens. Moreover, mutations in the SIV β3-β5 loop lead to greater spontaneous dissociation of gp120 from cell-associated trimers. We suggest that the CD4-induced rearrangement of this loop releases structural constraints on gp41 and thus potentiates its fusion activity.

TI Restraining the conformation of HIV-1 gp120 by removing a flexible loop
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1328398 CAPLUS
DOCUMENT NUMBER: 144:68577
TITLE: Env polypeptide complexed with CD4 mimetics to induce production of neutralizing antibodies against AIDS and disorders related to HIV infection
INVENTOR(S): Srivastava, Indresh K.; Sharma, Victoria; Barnett, Susan W.; Ulmer, Jeffrey
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 91 pp., which
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005121175	A2	20051222	WO 2005-US22808	20050608
WO 2005121175	A9	20060316		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,

RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2570043	A1	20051222	CA 2005-2570043		20050608
EP 1773880	A2	20070418	EP 2005-786186		20050608
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU					
IN 2006KN03593	A	20070615	IN 2006-KN3593		20061130
PRIORITY APPLN. INFO.:			US 2004-578211P	P	20040608
			US 2004-578445P	P	20040608
			WO 2005-US22808	W	20050608

OTHER SOURCE(S): MARPAT 144:68577

AB Provided herein are small mol. CD4 mimetics complexed with HIV env proteins (gp120, gp140 and gp160) through linking or crosslinking moiety. A CD4 mimetic of the invention, when bound to an Env protein, is effective to induce a conformational change in the Env protein such that cyptic epitopes on the Env protein are exposed. Also provided herein are related methods of identifying and using such small mol. CD4 mimetics, for example, to elicit an immune response in a subject upon administration. The CD4 small mol. comprises a fused bicyclic or tricyclic core structure such as indole, pyrrolopyridine and fluoren-9-one.

TI Env polypeptide complexed with CD4 mimetics to induce production of neutralizing antibodies against AIDS and disorders related to HIV infection

L8 ANSWER 4 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2005:67481 CAPLUS
DOCUMENT NUMBER:	142:174907
TITLE:	Selective recognition of oligomeric HIV-1 primary isolate envelope glycoproteins by potently neutralizing ligands requires efficient precursor cleavage
AUTHOR(S):	Pancera, Marie; Wyatt, Richard
CORPORATE SOURCE:	Structural Virology Section, Vaccine Research Center, NIAID, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE:	Virology (2005), 332(1), 145-156 CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER:	Elsevier
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB A critical component of an effective HIV vaccine will be the induction of broadly neutralizing antibodies. Comprising the HIV spike, the exterior envelope glycoprotein gp120 and the transmembrane glycoprotein gp41 mediate receptor binding, viral entry, and are the targets for neutralizing antibodies. The gp120 and gp41 glycoproteins are derived from the gp160 precursor glycoprotein and following gp160 glycosylation, oligomerization and cleavage in the endoplasmic reticulum and Golgi, remain as non-covalently associated trimers of heterodimers. Previously, using cell-surface envelope glycoproteins derived from infection of a laboratory-adapted HIV-1 strain, a correlation had been established between the binding of gp120-directed antibodies to the viral glycoprotein and the ability of the antibodies to neutralize laboratory-adapted isolates. However, this has been more difficult to demonstrate for glycoproteins derived from primary patient isolates. Here, using a FACS-based method, the authors report that only gp120-directed neutralizing antibodies and the neutralizing ligand soluble CD4 efficiently bind to glycoproteins derived from the JR-FL primary isolate provided that the gp160 precursor protein is efficiently cleaved. Precursor cleavage was demonstrated by

cell-surface biotinylation and Western blotting. In stark contrast, both non-neutralizing and neutralizing antibodies bind non-cleaved envelope glycoproteins from JR-FL and YU2 isolates. These data imply that significant changes in Env spike structure are dependent upon precursor gp160 cleavage and are consistent with a restricted-binding-to-Env model of neutralization. The data also have implications in regards to the use and design of non-cleaved envelope glycoprotein trimeric immunogens as a means to selectively and preferentially present neutralizing epitopes to the host immune system.

TI Selective recognition of oligomeric HIV-1 primary isolate envelope glycoproteins by potently neutralizing ligands requires efficient precursor cleavage

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:142990 CAPLUS
DOCUMENT NUMBER: 140:180126
TITLE: Vaccine compositions comprising HIV envelope protein and CD4 for generating monoclonal anti-HIV antibodies and for immunotherapies
INVENTOR(S): Lusso, Paolo; Burastero, Samuele E.
PATENT ASSIGNEE(S): Fondazione Centro San Raffaele Del Monte Tabor, Italy
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014420	A1	20040219	WO 2003-IB3665	20030812
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2497662	A1	20040219	CA 2003-2497662	20030812
AU 2003253187	A1	20040225	AU 2003-253187	20030812
EP 1545602	A1	20050629	EP 2003-784418	20030812
EP 1545602	B1	20080507		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
AT 394116	T	20080515	AT 2003-784418	20030812
US 20060142219	A1	20060629	US 2005-524549	20050913
PRIORITY APPLN. INFO.:			GB 2002-18817 A	20020813
			WO 2003-IB3665 W	20030812

AB (A) Pharmaceutical composition for treating/preventing HIV comprising (i) a polynucleotide encoding HIV envelope protein and (ii) a polynucleotide encoding CD4 receptor protein or; (i) a polynucleotide encoding HIV envelope protein and (ii) a CD4 receptor protein or; a fixed cell expressing an HIV envelope protein complexed with a CD4 receptor protein also disclosed are (B) pharmaceutical compns. for treating/preventing HIV comprising an antibody immunospecific for a fixed cell expressing an HIV envelope protein complexes

with a CD4 receptor protein. The binding of the CD4 to the HIV envelope protein, i.e. gp120 (or gp160), exposes hidden epitopes that may be used as targets in immunotherapies; the presentation of the gp120 and CD4 in the present forms is said to overcome problems with prior art soluble gp120-CD4 complexes. Also disclosed are genetic vectors encoding and expression HIV-1 gp120 and CD4 or their fusion protein for treating T or CD4+ T cell-mediated immune diseases and inflammation.

TI Vaccine compositions comprising HIV envelope protein and CD4 for generating monoclonal anti-HIV antibodies and for immunotherapies

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:813122 CAPLUS
DOCUMENT NUMBER: 134:127483
TITLE: Expression, purification, and characterization of gp160e, the soluble, trimeric ectodomain of the simian immunodeficiency virus envelope glycoprotein, gp160
AUTHOR(S): Chen, Bing; Zhou, Genfa; Kim, Mikyung; Chishti, Yasmin; Hussey, Rebecca E.; Ely, Barry; Skehel, John J.; Reinherz, Ellis L.; Harrison, Stephen C.; Wiley, Don C.
CORPORATE SOURCE: Laboratory of Molecular Medicine, The Children's Hospital, Howard Hughes Medical Institute, Boston, MA, 02215, USA
SOURCE: Journal of Biological Chemistry (2000), 275(45), 34946-34953
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The envelope glycoprotein, gp160, of simian immunodeficiency virus (SIV) shares .apprx.25% sequence identity with gp160 from the human immunodeficiency virus, type I, indicating a close structural similarity. As a result of binding to cell surface CD4 and co-receptor (e.g. CCR5 and CXCR4), both SIV and human immunodeficiency virus gp160 mediate viral entry by membrane fusion. We report here the characterization of gp160e, the soluble ectodomain of SIV gp160. The ectodomain has been expressed in both insect cells and Chinese hamster ovary (CHO)-Lec3.2.8.1 cells, deficient in enzymes necessary for synthesizing complex oligosaccharides. Both the primary and a secondary proteolytic cleavage sites between the gp120 and gp41 subunits of gp160 were mutated to prevent cleavage and shedding of gp120. The purified, soluble glycoprotein is shown to be trimeric by chemical crosslinking, gel filtration chromatog., and anal. ultracentrifugation. It forms soluble, tight complexes with soluble CD4 and a number of Fab fragments from neutralizing monoclonal antibodies. Soluble complexes were also produced of enzymically deglycosylated gp160e and of gp160e variants with deletions in the variable segments.

TI Expression, purification, and characterization of gp160e, the soluble, trimeric ectodomain of the simian immunodeficiency virus envelope glycoprotein, gp160

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1999:464186 CAPLUS
DOCUMENT NUMBER: 131:82951
TITLE: Method for inhibiting CD95-independent apoptosis in AIDS
INVENTOR(S): Krammer, Peter H.; Berndt, Christina
PATENT ASSIGNEE(S): Deutsches Krebsforschungszentrum Stiftung des Oeffentlichen Rechts, Germany
SOURCE: PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9936091	A2	19990722	WO 1999-DE109	19990115
WO 9936091	A3	19990916		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19801265	C1	19990812	DE 1998-19801265	19980115
EP 1049490	A2	20001108	EP 1999-907249	19990115
EP 1049490	B1	20020731		
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE				
JP 2002509118	T	20020326	JP 2000-539864	19990115
AT 221389	T	20020815	AT 1999-907249	19990115
ES 2181396	T3	20030216	ES 1999-907249	19990115
US 6485929	B1	20021126	US 2000-600522	20001011

PRIORITY APPLN. INFO.: DE 1998-19801265 A 19980115
WO 1999-DE109 W 19990115

AB Depletion of CD4+ T-cells in patients with AIDS occurs either (a) by a CD95-dependent mechanism in which apoptosis results from activation of CD95 receptors in the presence of HIV glycoprotein gp120 or (b) by a CD95-independent mechanism in which apoptosis results from binding of gp120 to CD4 and/or CXCR4 receptors. CD95-independent apoptosis is inhibited by blocking the binding of gp120, or of a factor which competes for this binding, to CD4 and/or CXCR4 receptors, and/or by inhibiting the signal path induced by such binding. Binding competitors may include antibodies to CD4 or CXCR4 receptors, HIV gp160, an MHC mol. (CD4 ligand), or stromal cell-derived factor 1α (SDF-1α, a CXCR4 ligand). Inhibitors of the signal path may include compds. which inhibit the loss of membrane asymmetry or the condensation of chromatin. A system for identifying substances which can be utilized for inhibiting CD95-independent apoptosis comprises (a) CD4+ or CXCR4+ cells, (b) HIV-1 gp120 or a factor which competes with gp120 for binding to CD4 or CXCR4, (c) a test substance, and preferably (d) a control substance with known inhibitory activity. Thus, HPB-ALL cells (CD4+/CXCR4+/CD95-), incubated with mouse anti-CXCR4 antibodies and then with sheep anti-mouse antibodies, underwent CD95-independent apoptosis; apoptosis was prevented by prior incubation of the cells with 250 nM SDF-1α.

TI Method for inhibiting CD95-independent apoptosis in AIDS

L8 ANSWER 8 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:60412 CAPLUS
DOCUMENT NUMBER: 130:236164
TITLE: Binding of CD4 ligands induces tyrosine phosphorylation of phosphatidylinositol-3 kinase p110 subunit

AUTHOR(S): Mazerolles, Fabienne; Fischer, Alain
CORPORATE SOURCE: INSERM U429, Hopital Necker-Enfants Malades, Paris, 75743, Fr.
SOURCE: International Immunology (1998), 10(12), 1897-1905
CODEN: INIMEN; ISSN: 0953-8178
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have previously reported that different putative CD4 ligands (anti-CD4 antibody, gp160 from HIV, synthetic peptides analogous to the residues 35-46 of HLA class II β1 chain and residues 134-148 of HLA class II β2 chain) down-regulate LFA-1-dependent adhesion between CD4+ T cells and HLa class II+ B cells, and also activate p56lck and the phosphatidylinositol-3 kinase (PI3-kinase) associated with the CD4-p56lck complex. It was demonstrated that the latter activation was dependent on the CD4-p56lck association Since these results suggest a relationship between p56lck and PI3-kinase, we investigated whether PI3-kinase was tyrosine phosphorylated after CD4 binding and whether this phosphorylation was also dependent on the CD4-p56lck association We show herein that CD4 binding increased tyrosine phosphorylation of the catalytic subunit p110 of PI3-kinase but not of the p85 subunit. Association between p56lck and PI3-kinase was constitutive, and was not modified after CD4 binding. In contrast, p110 tyrosine phosphorylation was inducible, transient and dependent on the CD4 -p56lck association The role of the tyrosine phosphorylation of p110-PI3-kinase following ligand binding to CD4 is unknown. We speculate that this event could link the activation of p56lck and of PI3-kinase after CD4 binding.
TI Binding of CD4 ligands induces tyrosine phosphorylation of phosphatidylinositol-3 kinase p110 subunit
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:523169 CAPLUS
DOCUMENT NUMBER: 129:229084
ORIGINAL REFERENCE NO.: 129:46577a,46580a
TITLE: The human immunodeficiency virus-1 envelope protein gp120 binds through its V3 sequence to the glycine site of N-methyl-D-aspartate receptors mediating noradrenaline release in the hippocampus
AUTHOR(S): Pattarini, R.; Pittaluga, A.; Raiteri, M.
CORPORATE SOURCE: Department of Experimental Medicine, Pharmacology and Toxicology Section, University of Genoa, Genoa, 16148, Italy
SOURCE: Neuroscience (Oxford) (1998), 87(1), 147-157
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent results show that the HIV-1 protein gp120 can enhance N-methyl-D-aspartate receptor-mediated release of noradrenaline from CNS nerve endings. The authors now investigate the mechanism of this action, including the structural determinants of the gp120 effect and the nature of its binding sites. The N-methyl-D-aspartate-evoked release of [3H]noradrenaline from rat hippocampal synaptosomes was potentiated similarly by gp120 and gp160; gp41 was ineffective. The regions of gp120 involved appear to be outside the CD4-binding domain of the protein, because gp120 retained its activity after pretreatment with N-carbomethoxycarbonyl-D-prolyl-D-phenylalanine, a compound known to inhibit

binding of gp120 to CD4 receptors. Moreover, sequences of gp120 critical for binding to CD4 did not mimic the effect of gp120. Preincubation of synaptosomes with anti-galactocerebroside antibodies did not affect gp120 activity. The protein effect was retained by peptides mimicking its V3 sequence, including the cyclic V3 "universal peptide" and the linear V3 sequence BRU-C-34-A, but not RP-135 (a central portion of BRU-C-34-A). The block of the N-methyl-D-aspartate-induced [3H]noradrenaline release by 7-chlorokynurenate, an antagonist at the N-methyl-D-aspartate receptor glycine site, was competitively reversed by glycine, by V3 and by BRU-C-34-A. When added with N-methyl-D-aspartate, V3 was three to four orders of magnitude more potent than glycine (EC50 values: about 20 pM and 150 nM, resp.) in enhancing [3H]noradrenaline release. Gp120 did not release glycine or serine from synaptosomes, thus excluding indirect actions through these agents. To conclude, gp120 may act following recognition by its V3 sequence of a high-affinity site possibly coincident with the glycine site of N-methyl-D-aspartate receptors present on hippocampal terminals of noradrenergic neurons. Considering the importance of N-methyl-D-aspartate receptor activation and of noradrenaline in cognitive processes, the effects of gp120 and V3 described here may be relevant to the pathol. of AIDS dementia.

TI The human immunodeficiency virus-1 envelope protein gp120 binds through its V3 sequence to the glycine site of N-methyl-D-aspartate receptors mediating noradrenaline release in the hippocampus

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 10 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1998:77365 CAPLUS
DOCUMENT NUMBER: 128:166233
ORIGINAL REFERENCE NO.: 128:32755a,32758a
TITLE: Cells transfected with a non-neutralizing antibody gene are resistant to HIV infection: targeting the endoplasmic reticulum and trans-Golgi network
AUTHOR(S): Zhou, Paul; Goldstein, Simoy; Devadas, Krishnakumar; Tewari, Deepanker; Notkins, Abner Louis
CORPORATE SOURCE: National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Journal of Immunology (1998), 160(3), 1489-1496 CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Plasmids containing single chain Fv (scFv) non-neutralizing human anti-HIV-1 gp41 Ab cDNA, with or without endoplasmic reticulum (ER) or trans-Golgi network (TGN) retention signals, were constructed. Stable transfectants expressing these scFvs then were generated from COS-7 cells and HIV-1-susceptible CD4+ human T cells (Jurkat). ScFv without a retention signal was secreted from cells, whereas scFv with an ER or TGN retention signal remained primarily within targeted intracellular compartments. The expression of scFv, scFv-ER, and scFv-TGN did not adversely affect the appearance of uninfected cells, as measured by growth rate or CD4 expression. Pulse-chase expts. revealed that the t1/2, of scFv-ER and scFv-TGN within cells was >24 h and <9 h, resp. The scFv-ER and scFv-TGN bound HIV gp160, and the scFv-ER-gp160 and the scFv-TGN-gp160 complexes were stable within HIV-infected transfectants. Further studies revealed that the maturation processing of gp160 into gp120 and gp41 was blocked in the scFv-ER transfectants, but not in the scFv-TGN transfectants.

Moreover, HIV replication, as measured by p24, was inhibited by up to 99% in cells transfected with scFv-ER or scFv-TGN, but was not inhibited in cells transfected with the secretory form of scFv. Thus, targeting of non-neutralizing anti-HIV-1 Abs to specific intracellular compartments blocks HIV replication and represents a potential therapeutic strategy for protecting uninfected lymphopoietic stem cells from HIV-1-infected patients.

TI Cells transfected with a non-neutralizing antibody gene are resistant to HIV infection: targeting the endoplasmic reticulum and trans-Golgi network

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1997:13293 CAPLUS
DOCUMENT NUMBER: 126:102693
ORIGINAL REFERENCE NO.: 126:19821a,19824a
TITLE: CD4 ligands inhibit the formation of multifunctional transduction complexes involved in T cell activation
AUTHOR(S): Jabado, Nada; Pallier, Annaick; Le Deist, Francoise; Bernard, Frederic; Fischer, Alain; Hivroz, Claire
CORPORATE SOURCE: INSERM Unit 429, Necker-Enfants Malades Hospital, Paris, Fr.
SOURCE: Journal of Immunology (1997), 158(1), 94-103
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ligands binding to the CD4 mol. can inhibit TCR-mediated T cell activation. The authors have previously reported that transcription factors regulating the expression of the IL-2 gene, NF-AT, NF-κB, and AP-1, are targets of this inhibitory effect in an in vitro model using peripheral human CD4+ T cells activated by a CD3 mAb. Two T cell activation pathways involved in the regulation of these transcription factors, calcium flux and the p21ras pathway, were investigated as potential targets. Binding of HIV envelope glycoprotein gp160 /gp120 or a CD4 mAb to the CD4+ T cells, prior to TCR/CD3 activation, inhibited the intracellular calcium elevation. This event strongly suggested an inhibition of PLCγ1 activity. Tyrosine phosphorylation of PLCγ1, induced by CD3 activation, was not affected, but its association with tyrosine-phosphorylated proteins, including a 62-kDa protein, was disrupted. This PLCγ1-associated p62 was immunoreactive to p62-Sam68 Absolute The activation-induced phosphorylation of two p21ras effectors, Raf-1 and Erk2, was inhibited by the CD4 ligands, indirectly pointing to inhibition of the p21ras activation pathway. In addition, the authors demonstrate that TCR activation of normal CD4+ T cells induced the formation of p120GAP and PLCγ1-containing complexes. These complexes also contain other unidentified proteins. CD4 ligand binding induced a defective formation of these transduction complexes. This may result in inefficient signaling, partially accounting for the inhibitory effects of the CD4 ligands on both p21ras and calcium-activation pathways.

TI CD4 ligands inhibit the formation of multifunctional transduction complexes involved in T cell activation

L8 ANSWER 12 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:730661 CAPLUS
DOCUMENT NUMBER: 126:17578
ORIGINAL REFERENCE NO.: 126:3657a,3660a

TITLE: Complement-activating antibodies in sera from infected individuals and vaccinated volunteers that target human immunodeficiency virus type 1 to complement receptor type 1 (CR1, CD35)
AUTHOR(S): Zhou, Jintao; Montefior, David C.
CORPORATE SOURCE: Department Surgery, Duke Univ. Medical Center, Durham, NC, 27710, USA
SOURCE: Virology (1996), 226(1), 13-21
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Complement receptor type 1 (CR1) plays a central role in clearing immune complexes from the circulation and probably contributes to the retention of immune complexes on the surface of follicular dendritic cells. Virus-specific, complement-activating antibodies can target human immunodeficiency virus type 1 (HIV-1) to CR1-bearing cells but the potential impact that these antibodies have on HIV-1 pathogenesis is unknown. To study these antibodies, an assay was developed in which immune complexes containing HIV-1, antibody, and complement were formed in vitro and captured on the surface of 96-well immunoplates coated with recombinant soluble human CR1 (rsCR1). Captured virus was detected by p24 immunoassay or by infection of human CD4+ lymphocytes. Two laboratory strains of HIV-1 (IIIB and MN) and primary isolates could be captured using sera from infected individuals or vaccinated volunteers as a source of complement-activating antibodies. HIV-1 immune complexes captured by solid-phase rsCR1 could be transferred to MT-2 cells for productive infection. Antibodies had no activity in this assay when the normal human serum used as a source of complement had been heat-inactivated or depleted of complement component C3, confirming a requirement for complement. These complement-activating antibodies in sera from infected individuals showed strong cross-reactivity with HIV-1 IIB, MN, and a heterologous primary isolate, but reacted poorly with the autologous isolate obtained at the time of serum collection. Average titers of these antibodies measured with HIV-1 IIB were moderately lower in HIV-1-infected progressors compared to nonprogressors. In contrast to sera from infected individuals, sera from gp160IIB-vaccinated volunteers showed specificity for the vaccine strain of virus. These results provide supporting evidence that envelope-specific, complement-activating antibodies induced by infection or gp160 immunization can target HIV-1 immune complexes to CR1. In addition, they demonstrate that such antibodies may sometimes be type-specific and that HIV-1 immune complexes bound to CR1 are infectious.

TI Complement-activating antibodies in sera from infected individuals and vaccinated volunteers that target human immunodeficiency virus type 1 to complement receptor type 1 (CR1, CD35)

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 13 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:453732 CAPLUS
DOCUMENT NUMBER: 125:140312
ORIGINAL REFERENCE NO.: 125:26273a,26276a
TITLE: Influence of N-linked glycans in V4-V5 region of human immunodeficiency virus type 1 glycoprotein gp160 on induction of a virus-neutralizing humoral response
AUTHOR(S): Bolmstedt, Anders; Sjoelander, Sigrid; Hansen, John-Erik S.; Akerblom, Lennart; Hemming, Anna; Hu, Shiu-Lok; Morein, Bror; Olofsson, Sigvard

CORPORATE SOURCE: Department Clinical Virology, University Goteborg, Goeteborg, S-413 46, Swed.
SOURCE: Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology (1996), 12(3), 213-220 CODEN: JDSRET; ISSN: 1077-9450
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English

AB One of the functions of N-linked glycans of viral glycoproteins is protecting otherwise accessible neutralization epitopes of the viral envelope from neutralizing antibodies. The aim of the present study was to explore the possibility to obtain a more broadly neutralizing immune response by immunizing guinea pigs with gp160 depleted of three N-linked glycans in the CD4-binding domain by site-directed mutagenesis. Mutant and wild type gp160 were formulated into immunostimulating complexes and injected s.c. into guinea pigs. Both prepns. induced high serum antibody response to native gp120 and V3 peptides. Both prepns. also induced antibodies that bound equally well to the V3 loop or the CD4-binding region, as determined by a competitive ELISA. The sera from animals, immunized with mutated glycoprotein, did not neutralize nonrelated HIV strains better than did sera from animals, immunized with wild type glycoprotein. Instead, a pattern of preferred homologous neutralization was observed, i.e., sera from animals, immunized with mutant gp160, neutralized mutant virus better than wild type virus, and vice versa. These data indicated that elimination of the three N-linked glycans from gp160 resulted in an altered local antigenic conformation but did not uncover hidden neutralization epitopes, broadening the immune response.

TI Influence of N-linked glycans in V4-V5 region of human immunodeficiency virus type 1 glycoprotein gp160 on induction of a virus-neutralizing humoral response

L8 ANSWER 14 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:299494 CAPLUS
DOCUMENT NUMBER: 125:5197
ORIGINAL REFERENCE NO.: 125:1179a,1182a
TITLE: Folding, assembly, and intracellular trafficking of the human immunodeficiency virus type 1 envelope glycoprotein analyzed with monoclonal antibodies recognizing maturational intermediates
AUTHOR(S): Ottenken, Ahlert; Earl, Patricia L.; Moss, Bernard
CORPORATE SOURCE: Laboratory Viral Diseases, National Institute Allergy Infectious Diseases, Bethesda, MD, 20892-0455, USA
SOURCE: Journal of Virology (1996), 70(6), 3407-3415 CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Monoclonal antibodies (MAbs) that bind linear or conformational epitopes on monomeric or oligomeric human immunodeficiency virus type 1 (HIV-1) envelope glycoproteins were screened for their recognition of maturational intermediates. On the basis of reactivities with gp160 at different times after pulse-labeling, the MAbs were sorted into groups that exhibited binding which was immediate and constant, immediate but transient, delayed, late, or very late. This grouping was consistent with the selectivity of the MAbs for structural features of gp160. Thus, a MAb to the V3 loop reacted with envelope proteins at all times, in accord with the relative conformational independence and accessibility of the epitope. Several MAbs that preferentially react with

monomeric gp160 exhibited diminished binding after the pulse. A 10-min lag occurred before gp160 reacted with conformational MAbs that inhibited CD4 binding. The availability of epitopes for other conformational MAbs, including some that react equally with monomeric and oligomeric gp160 and some that react better with oligomeric forms, was half-maximal in 30 min and closely followed the kinetics of gp160 oligomerization. Remarkably, there was a 1- to 2-h delay before gp160 reacted with stringent oligomer-specific MAbs. After 4 h, approx. 20% of the gp160 was recognized by these MAbs. Epitopes recognized by monomer-specific or CD4-blocking MAbs but not by oligomer-dependent MAbs were present on gp160 mols. associated with the mol. chaperone BiP/GRP78. MAbs with a preference for monomers reacted with recombinant or HIV-1 envelope proteins in the endoplasmic reticulum, whereas the oligomer-specific MAbs recognized them in the Golgi complex. Addnl. information regarding gp160 maturation and intracellular trafficking was obtained by using brefeldin A, dithiothreitol, and a low temperature

TI Folding, assembly, and intracellular trafficking of the human immunodeficiency virus type 1 envelope glycoprotein analyzed with monoclonal antibodies recognizing maturational intermediates

L8 ANSWER 15 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	1996:227291 CAPLUS
DOCUMENT NUMBER:	124:286368
ORIGINAL REFERENCE NO.:	124:53039a,53042a
TITLE:	Brucella abortus conjugated with a peptide derived from the V3 loop of human immunodeficiency virus (HIV) type 1 induces HIV-specific cytotoxic T-cell responses in normal and in CD4+ cell-depleted BALB/c mice
AUTHOR(S):	Lapham, Cheryl; Golding, Basil; Inman, John; Blackburn, Robert; Manischewitz, Jody; Highet, Patricia; Golding, Hana
CORPORATE SOURCE:	Lab. Retrovirus Res., Natl. Inst. Allergy Infectious Dis., Bethesda, MD, 20892, USA
SOURCE:	Journal of Virology (1996), 70(5), 3084-92 CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER:	American Society for Microbiology
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB The authors have previously shown that immunization of mice with human immunodeficiency virus (HIV)-derived proteins or peptides conjugated to inactivated Brucella abortus induces the secretion of virus-neutralizing antibodies, predominantly of the IgG2a isotype. In addition, B. abortus activates human CD4+ and CD8+ cells to secrete gamma interferon. Since these are both characteristics of a Th1-type immune response, which is associated with the development of cell-mediated immunity, it was important to determine if B. abortus conjugates would also act as a carrier to induce a cytotoxic T-lymphocyte (CTL) response. To test this hypothesis, the authors conjugated an 18-amino-acid peptide from the V3 loop of the MN strain of HIV-1 gp120 that contains both B- and cytotoxic T-cell epitopes to B. abortus (B. abortus-MN 18-mer). A 10-amino-acid fragment of this peptide has been shown to be the minimal CTL determinant presented by murine H-2Dd. It was found that two in vivo immunizations with 108 organisms of B. abortus-MN 18-mer followed by in vitro stimulation with peptide induced a virus-specific CTL response. Conjugation to B. abortus was required for in vivo priming, since there was no induction of memory CTLs when B. abortus was only mixed with peptide. Targets pulsed with peptide as well as those infected with a vaccinia virus encoding HIV gp160 were killed, demonstrating recognition of naturally processed envelope. Also, major histocompatibility complex-incompatible L cells which were

infected with vaccinia viruses that encoded H-2Dd, but not H-2Kd, and pulsed with peptide were lysed. This demonstrated the appropriate major histocompatibility complex class I restriction. Treatment of the mice with anti-L3T4 prior to immunization caused a severe depletion of CD4+ lymphocytes, yet it did not decrease the CTL priming. Thus, inactivated B. abortus can induce non-CD4+ cells to produce the cytokines required for CTL induction. The authors conclude that B. abortus stimulates a cellular as well as a humoral immune response, even in the relative absence of CD4+ helper cells. It may be a particularly useful vaccine carrier in HIV-1-infected individuals or others with impaired CD4+ T-cell function.

TI Brucella abortus conjugated with a peptide derived from the V3 loop of human immunodeficiency virus (HIV) type 1 induces HIV-specific cytotoxic T-cell responses in normal and in CD4+ cell-depleted BALB/c mice

=> D L8 IBIB ABS 16-26

L8 ANSWER 16 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	1995:758307 CAPLUS
DOCUMENT NUMBER:	123:141593
ORIGINAL REFERENCE NO.:	123:25213a,25216a
TITLE:	HIV-1 envelope glycoproteins induce activation of activated protein-1 in CD4+ T cells
AUTHOR(S):	Chirmule, Narendra; Goonewardena, Harris; Pahwa, Sunil; Pasieka, Regina; Kalyanaraman, Vaniambadi S.; Pahwa, Savita
CORPORATE SOURCE:	Med. Coll., Cornell Univ., Manhasset, NY, 11030, USA
SOURCE:	Journal of Biological Chemistry (1995), 270(33), 19364-9 CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER:	American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Activation of CD4 pos. T cells is a primary requirement for human immunodeficiency virus (HIV) entry, efficient HIV replication, and progression to AIDS. Utilizing CD4 pos. T cell lines and purified T cells from normal individuals, the authors have demonstrated that native envelope glycoproteins of HIV, gp160, can induce activation of transcription factor, activated protein-1 (AP-1). The stimulatory effects of gp160 are mediated through the CD4 mol., since treatment of gp160 with soluble CD4 -IgG abrogates its activity, and CD4 neg. T cell lines fail to be stimulated with gp160. Immunopptn. of the gp160 -induced nuclear exts. with polyclonal antibodies to Fos and Jun proteins indicates that AP-1 complex is comprised of members of these family of proteins. The gp160-induced AP-1 complex is dependent upon protein tyrosine phosphorylation and is protein synthesis-independent. This stimulation can also be abolished by inhibitors of protein kinase C, but it is unaffected by calcium channel blocker or cyclosporine A. This gp160 treatment adversely affects the functional capabilities of T cells; pretreatment of CD4+ T cells with gp160 for 4 h at 37° inhibited anti-CD3-induced interleukin-2 secretion. Effects similar to gp160 were seen with anti-CD4 mAb. The aberrant activation of AP-1 by gp160 in CD4 pos. T cells could result in up-regulation of cytokines containing AP-1 sites, e.g. interleukin-3 and granulocyte macrophage colony-stimulating factor, and concurrently lead to T cell unresponsiveness by inhibiting interleukin-2 secretion.

L8 ANSWER 17 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:640033 CAPLUS
DOCUMENT NUMBER: 123:54086
ORIGINAL REFERENCE NO.: 123:9735a,9738a
TITLE: Attachment of an oligopeptide epitope to the C-terminus of recombinant SIV gp160 facilitates the construction of SMAA complexes while preserving CD4 binding
AUTHOR(S): Hanke, T.; Young, D. F.; Doyle, C.; Jones, I.; Randall, R. E.
CORPORATE SOURCE: Div. Cell Mol. lBiology, Univ. St. Andrews, St. Andrews, KY16 9AL, UK
SOURCE: Journal of Virological Methods (1995), 53(1), 149-56
CODEN: JVMEDH; ISSN: 0166-0934
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A small 14 amino acid oligopeptide tag (termed SV5-Pk) was fused onto the carboxy-terminus of simian immunodeficiency virus gp160 expressed from a recombinant baculovirus. The presence of the Pk tag had no obvious effect on the expression and glycosylation of gp160 and did not interfere either with CD4 binding or with cleavage at its maturation site by the protease furin. The presence of the Pk tag did, however, facilitate the simplified purification of full-length gp160 and its incorporation into immunogenic solid matrix-antibody-antigen (SMAA) complexes.

L8 ANSWER 18 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:209260 CAPLUS
TITLE: Syngeneic adoptive transfer of anti-human immunodeficiency virus-1 (HIV-1)-primed lymphocytes from a vaccinated HIV-seronegative individual to his HIV-1-infected identical twin
AUTHOR(S): Bex, F.; Hermans, P.; Sprecher, S.; Achour, A.; Badjou, R.; Desgranges, C.; Cogniaux, J.; Franchioli, P.; Vanhulle, C.; et al.
CORPORATE SOURCE: Dept. Mol. Biology, Univ. Brussels, Brussels, Belg.
SOURCE: Blood (1994), 84(10), 3317-26
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Immunotherapy by adoptive transfer of lymphocytes was attempted in identical twins, one who was virus-free and the other who was infected with human immunodeficiency virus-1 (HIV-1), at the stage of acquired immunodeficiency syndrome. The noninfected twin was vaccinated by priming with a recombinant vaccinia virus expressing the envelope glycoprotein of one of his brother's viruses and boosting with the same purified gp160 adsorbed on alum. Vacciniation elicited major histocompatibility complex class I-restricted CD8+ cytolytic T lymphocytes specific for HIV-1, but no antibody response. The diseased brother, a 38-yr-old homosexual who had developed repeated opportunistic infections since 1990 and had a CD4+ count reduced to practically zero, was treated by infusions of lymphocytes collected from the vaccinated brother by lymphopheresis. After a first transfer of the whole lymphocyte population, no changes were observed in the clin. status and biol. or virol. parameters. A second transfer was then applied with activation of the cells with purified envelope glycoprotein before infusion. The outcome of the treatment was an increase in total lymphocytes, in CD4+ and activated CD8+ DR+ cell counts, and in proliferative responses to HIV antigens. A marked but transient 3-log

increase in cellular and plasmatic virus loads was also observed after the second adoptive transfer. These observations will be considered with attention to improve the future adoptive transfer protocols, especially in patients with severe CD4+ depletion.

L8 ANSWER 19 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:577522 CAPLUS
DOCUMENT NUMBER: 121:177522
ORIGINAL REFERENCE NO.: 121:32239a,32242a
TITLE: Surface expression of the HIV-1 envelope proteins in env gene-transfected CD4-positive human T cell clones: Characterization and killing by an antibody -dependent cellular cytotoxic mechanism
AUTHOR(S): Ahmad, Ali; Yao, Xiao A.; Tanner, Jerome E.; Cohen, Eric; Menezes, Jose
CORPORATE SOURCE: Ste-Justine Hospital, University Montreal, Montreal, QC, H3T 1C5, Can.
SOURCE: Journal of Acquired Immune Deficiency Syndromes (1994), 7(8), 789-98
CODEN: JAISET; ISSN: 0894-9255
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The env gene of the human immunodeficiency virus-type 1 (HIV-1) was transfected in CEM-nkr, a human lymphoid cell line of T lineage that is resistant to the activity of natural killer cells, and for the first time, transfected T cell clones were established that stably express gp160 intracellularly and gp120 on the surface as demonstrated by radioimmunopptn. as well as by indirect membrane immunofluorescence. The regulatory protein vpu was not detected by radioimmunopptn. in these clones. The surface expression of gp120 without vpu in these clones provides direct evidence that gp160 is processed and cleaved (without vpu) in CD4+ cells. The CD4 antigens of these cells copptd. gp160; interestingly, no reduction of the surface CD4 expression (detectable by flow cytometric anal. of membrane immunofluorescence with OKT4) in the transfected cells was observed However, decreased reactivity of the transfected clones with OKT4A was observed The gp120-expressing cells did not form syncytia on coculture with other CD4+ human cell lines. These observations suggest the binding of gp120 to the surface CD4 antigen of the transfected cells. The transfected cells retained their resistance to the activity of the natural killer cells but showed a significant lysis when they were preincubated with AIDS patients' serum containing anti-gp120/41 antibodies. Thus, the expressed gp120/41 in these cells made them susceptible to killing by an antibody-dependent cellular cytotoxicity (ADCC) mechanism. To the authors knowledge, these are the first reported CD4+ T cell lines that stably express HIV envelope proteins. These cell lines would be useful as targets in exploring gp120/41-specific immune responses, especially in conducting gp120/41-specific ADCC studies in HIV-infected or gp120/41 (gp160)-vaccinated individuals.

L8 ANSWER 20 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:532082 CAPLUS
DOCUMENT NUMBER: 121:132082
ORIGINAL REFERENCE NO.: 121:23873a,23876a
TITLE: Adhesion mediated by intercellular adhesion molecule 1 attenuates the potency of antibodies that block HIV-1 gp160-dependent syncytium formation
AUTHOR(S): Berman, Phillip W.; Nakamura, Gerald R.
CORPORATE SOURCE: Department Immunology, Genentech, Inc., South San Francisco, CA, 94080, USA

SOURCE: AIDS Research and Human Retroviruses (1994), 10(5), 585-93
CODEN: ARHRE7; ISSN: 0889-2229
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several lines of evidence suggest that leukocyte adhesion mols. can promote HIV-1-mediated cell fusion and syncytium formation. In the present studies, the human kidney cell line, 293, was transfected with the envelope glycoprotein gene of the MN strain of HIV-1 alone or cotransfected with a cDNA encoding intercellular adhesion mol. 1 (ICAM-1). It was found that 293 cells transfected with the HIV-1MN env gene expressed the HIV-1 polyglycoprotein precursor, gp160, and the mature gp120-gp41 complex. When mixed with a CD4+ T cell line (CEM), the gp160-transfected cells mediated heterotypic cell fusion and formed multinucleate syncytia. Virus-neutralizing monoclonal antibodies to the V2 and V3 domains of gp120 were able to inhibit syncytium formation, as were monoclonal antibodies to CD4. When ICAM-1 was coexpressed with gp160, syncytium formation between the transfected kidney cells and uninfected CD4+ T cells was markedly enhanced. Inhibitors of HIV-1 infectivity (e.g., monoclonal antibodies to gp120, recombinant soluble CD4) were able to prevent syncytium formation; however, the syncytium-blocking activity of these agents was significantly attenuated in cultures in which ICAM-1 was cotransfected with gp160. These results confirm that leukocyte adhesion mols. can promote gp160-mediated syncytium formation and demonstrate, for the first time, that adhesive interactions mediated by ICAM-1 and its contrareceptor, LFA-1, attenuate the syncytium-inhibiting activity of virus-neutralizing monoclonal antibodies and soluble CD4. These findings suggest that the type and magnitude of leukocyte adhesion mols. expressed on cells may be a significant variable in in vitro HIV-1 neutralization assays.

L8 ANSWER 21 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:455747 CAPLUS
DOCUMENT NUMBER: 121:55747
ORIGINAL REFERENCE NO.: 121:10043a,10046a
TITLE: Intracellular membrane traffic of human immunodeficiency virus type 1 envelope glycoproteins: Vpu liberates Golgi-targeted gp160 from CD4-dependent retention in the endoplasmic reticulum
AUTHOR(S): Kimura, Tominori; Nishikawa, Masao; Ohyama, Akio
CORPORATE SOURCE: Dep. Microbiol., Kansai Med. Univ., Moriguchi, 570, Japan
SOURCE: Journal of Biochemistry (Tokyo, Japan) (1994), 115(5), 1010-20
CODEN: JOBIAO; ISSN: 0021-924X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The membrane traffic of human immunodeficiency virus type 1 (HIV-1) envelope glycoproteins was investigated in COS-1 cells transiently expressing the HIV-1 env, vpu, and rev genes. Anal. of oligosaccharide processing revealed that the majority of gp160 remained fully Endo-H sensitive throughout a 21-h chase period, and hence cleavage of gp160 to gp120-gp41 took place prior to the creation of hybrid and complex oligosaccharides on gp120. Immunofluorescence microscopy demonstrated that in the absence of CD4 both gp160 and Vpu are targeted to the Golgi apparatus, which can be stained with wheat germ agglutinin or antibodies to the human KDEL receptor. In contrast, gp160 complexed with CD4 was retained in the

ER and thus failed to reach the cis-Golgi compartment. Although gp160-bound CD4 has its own half life of 4 h 35 min in the endoplasmic reticulum (ER), co-expression of Vpu accelerated the turnover of CD4 by 5.5-fold and thereby enabled gp160 to be translocated out of the ER to the cis-Golgi compartment. Thus, Vpu prevents the formation of stable CD4-gp160 to accumulate in the Golgi apparatus, where it is selectively retained to produce gp120-gp-41.

L8 ANSWER 22 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:455358 CAPLUS
DOCUMENT NUMBER: 121:55358
ORIGINAL REFERENCE NO.: 121:9947a,9950a
TITLE: Cell surface down-modulation of CD4 after infection by HIV-1
AUTHOR(S): Geleziunas, Romas; Bour, Stephane; Wainberg, Mark A.
CORPORATE SOURCE: McGill AIDS Centre, McGill University, Montreal, Can.
SOURCE: FASEB Journal (1994), 8(9), 593-600
CODEN: FAJOEC; ISSN: 0892-6638
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 66 refs. Entry of HIV-1 into host cells is generally mediated by the cell surface CD4 receptor after specific interaction with the viral envelope glycoprotein gp120. Infection by HIV-1 commonly leads to the disappearance of CD4 from the plasma membrane, a phenomenon referred to as receptor down-modulation. This, in turn, renders cells refractory to subsequent infection by the same or other viruses that use the CD4 receptor for entry, creating a state of superinfection immunity. CD4 down-modulation is a complex process involving a variety of viral gene products, the effects of which may be manifest at different stages within the viral replication cycle. CD4 disappearance from the cell surface occurs in each of the CD4+ lymphocytes, T-cell lines, monocytic cell lines, and monocyte-derived macrophages. Internalization of CD4 can occur after binding of either gp120 alone or gp120 antigen-antibody complexes, and may also be mediated by the HIV-1 Nef gene. Other factors that cause cell surface CD4 depletion include redns. in CD4 transcript levels, impaired translation of CD4 mRNA, formation of CD4-gp160 intracellular complexes, and degradation of CD4 mediated by the HIV-1 Vpu gene.

L8 ANSWER 23 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:189078 CAPLUS
DOCUMENT NUMBER: 120:189078
ORIGINAL REFERENCE NO.: 120:33421a,33424a
TITLE: Recombinant hepatitis B surface antigen as a carrier of human immunodeficiency virus epitopes
AUTHOR(S): Michel, M. L.; Mancini, M.; Schlienger, K.; Tiollais, P.
CORPORATE SOURCE: Unite Recomb. Expression Genet., Inst. Pasteur, Paris, 75724, Fr.
SOURCE: Research in Virology (1993), 144(4), 263-7
CODEN: RESVEY; ISSN: 0923-2516
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Eukaryotic cells transformed with a plasmid expression vector are able to synthesize and assemble HBsAg, a complex multimeric lipoprotein particle. Hybrid particles carrying HIV1 antigenic determinants were constructed and injected into monkeys. A complete immune response including neutralizing antibodies, proliferative and cytotoxic

T-cell activities was obtained. Thus, such HIV/HBsAg hybrid particles could be a new approach to multivalent vaccination.

L8 ANSWER 24 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:132199 CAPLUS
DOCUMENT NUMBER: 120:132199
ORIGINAL REFERENCE NO.: 120:23257a,23260a
TITLE: Evidence for the role of CR1 (CD35), in addition to CR2 (CD21), in facilitating infection of human T cells with opsonized HIV
AUTHOR(S): Delibrias, C. C.; Kazatchkine, M. D.; Fischer, E.
CORPORATE SOURCE: Hop. Broussais, Paris, 75014, Fr.
SOURCE: Scandinavian Journal of Immunology (1993), 38(2), 183-9
CODEN: SJIMAX; ISSN: 0300-9475
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Complement activation by HIV results in the binding of C3 fragments to the gp160 complex and enhanced infection of C3 receptor-bearing target cells. The authors have studied complement-mediated enhancement of infection of the human CD4 -pos. T-cell line HPB-ALL which expresses the CR1 (CD35) and CR2 (CD21) receptors for C3. CR1 and CR2 are present on 15% and 40% of normal peripheral blood CD4-pos. T lymphocytes resp. Opsonization of the virus with complement resulted in a 3-10 fold enhancement of infection of HPB-ALL cells, as assessed by measuring the release of p24 antigen in culture supernatants throughout the culture period. Blockade of CR2 with cross-linked anti-CR2 monoclonal antibodies decreased infection to the level observed with unopsonized virus. Blocking CR1 reduced complement-mediated infection by 50-80%. Expts. using serum deficient in complement factor I demonstrated that CR1 mediates the interaction between opsonized virus and T cells in addition to its ability to serve as a cofactor for the cleavage of C3b into smaller fragments that interact with CR2. A requirement for CD4 in complement-mediated enhancement of infection was observed with HIV-1 Bru but not with HIV-1 RF. Thus, CR1 and CR2 contribute in an independent and complementary fashion to penetration of opsonized virus into complement receptor-expressing T cells. Involvement of CD4 in infection with opsonized virus depends on the viral strain.

L8 ANSWER 25 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:75343 CAPLUS
DOCUMENT NUMBER: 120:75343
ORIGINAL REFERENCE NO.: 120:13559a,13562a
TITLE: Apoptosis induced in CD4+ cells expressing gp160 of human immunodeficiency virus type 1
AUTHOR(S): Lu, Yi Yu; Koga, Yasuhiro; Tanaka, Kazuo; Sasaki, Masafumi; Kimura, Genki; Nomoto, Kikuo
CORPORATE SOURCE: Med. Inst. Bioregul., Kyushu Univ., Fukuoka, 812, Japan
SOURCE: Journal of Virology (1994), 68(1), 390-9
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB , The authors previously demonstrated that the expression of gp160 , a precursor form of envelope glycoprotein of human immunodeficiency virus type 1, in CD4+ cells causes the downregulation of surface CD4 and single-cell killing by forming intracellular gp160 -CD4 complex. Here the authors investigated the events that lead to cell death in CD4+ cells expressing gp160. Apoptosis was induced in cells undergoing single-cell

death. Moreover, even the cell clone, which expresses so little gp160 that it does not exhibit any apparent cytopathic effects, such as the inhibition of cell growth, was highly susceptible to the apoptosis induction by the anti-Fas monoclonal antibody.

L8 ANSWER 26 OF 43 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:52430 CAPLUS
DOCUMENT NUMBER: 120:52430
ORIGINAL REFERENCE NO.: 120:9587a,9590a
TITLE: Non-covalent complexes of HIV gp120 with CD4 and/or mAbs enhance activation of gp120-specific T clones and provide intermolecular help for anti-CD4 antibody production
AUTHOR(S): Manca, Fabrizio; Seravalli, Egilde; Valle, Maria Teresa; Fenoglio, Daniela; Kunkl, Annalisa; Li Pira, Giuseppina; Zolla-Pazner, Susan; Celada, Franco
CORPORATE SOURCE: Dep. Immunol., Univ. Genoa, Genoa, 16132, Italy
SOURCE: International Immunology (1993), 5(9), 1109-17
CODEN: INIMEN; ISSN: 0953-8178
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The liaison between CD4 and gp120 that offers the first entry opportunity to HIV may also provoke perturbations of the immune control of the host with far-reaching immunopathol. consequences. The authors wondered whether a mechanism of intermol. help (T help across the gap of a non-covalent bond, in contrast to the intramol. help of carrier to hapten) could break self-tolerance and be the cause of the frequent anti-CD4 autoantibodies found in AIDS patients. To determine whether this hypothesis deserves further testing, the authors designed a series of in vitro and in vivo expts. of increasing complexity, focused on the presentation of gp120 to specific T cells by antigen presenting cells (APC) exposed to the envelope protein in the form of non-covalent complexes. Bi-mol. complexes were constructed by allowing gp120 or gp160 to bind specific human mAbs. Tri-mol. complexes were constructed by introducing CD4 as an intermediate ligand between gp120 and mouse mAbs specific for CD4 . In all cases the use of complexes did enhance the immunogenic capacity of substimulatory doses of gp120 or gp160 by facilitating uptake by APC via Fc receptor and consequent presentation to specific human T cell clones. Help for the production in vivo of anti-CD4 antibodies was obtained from T lymphocytes specific for gp120 when CD4-primed memory B cells were pulsed with CD4 complexed with gp120, thus demonstrating in the mouse the entire cycle of intermol. help via non-covalent interaction.

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